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AMENDED SPECIFICATION

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PATENT SPECIFICATION

NO DRAWINGS

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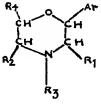
COMPLETE SPECIFICATION

Morpholine Compounds and their production

We, J. R. GEIGY A.-G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

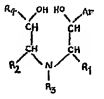
This invention relates to morpholine compounds and their production.

According to the present invention there is provided a process for the production of morpholine compounds having the general formula:



I

wherein Ar is an unsubstituted phenyl radical or a phenyl radical substituted by halogen atoms, alkyl, alkoxy or hydroxy groups, R_1 and R_2 are hydrogen atoms or alkyl radicals containing 1 to 4 carbon atoms, R_3 is a hydrogen atom or an alkyl or alkenyl radical containing 1 to 4 carbon atoms and R_4 is an araliphatic radical or an aliphatic radical which may contain oxygen or sulphur atoms as linking members or hydroxy groups as substituents; R_1 may also form together with the alkyl radical R_2 a divalent hydrocarbon radical, which comprises treating a compound of the general formula:



II

wherein Ar, R_1, R_2, R_3 and R_4 have the meanings given above, with a dehydrating agent.

It has been found that the compounds of the general formula I have valuable neurophysiological properties. In particular they stimulate the central nervous system without increasing blood pressure at the same time. On the contrary, some of the compounds cause a considerable reduction in the blood pressure. In addition the compounds defined above, particularly when they contain hydroxy groups in the radicals Ar and/or R_4, are valuable intermediate products for the production of other substances having a neurophysiological action.

Mineral acids for example, such as concentrated sulphuric acid or 48% hydrobromic acid are suitable as dehydrating agents. The ring is formed by sulphuric acid readily in the cold; if hydrobromic acid is used the reaction mixture must be heated. If hydroxy groups are contained in Ar, it is possible that the ring can be formed under considerably milder conditions, for example by dissolving hydrohalides of such compounds of the general formula II in alcohol and leaving the solution to stand or gently heating it. In this case

therefore, one mol, i.e. of the hydrogen halide bound in the hydrohalide, is sufficient as a dehydrating agent.

Compounds of the general formula II can be obtained for example by reacting a hydroxy amine of the general formula:

III

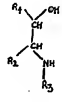
with an oxirane of the general formula:

IV

wherein Ar, R_1, R_2, R_3 and R_4 have the meanings given above. The crude products so obtained can be used direct for ring closure. The reactions can be performed in the presence or, what is generally more advantageous, in the absence of inert organic solvents at room temperature or in the warm; in the latter case low boiling oxiranes are reacted in a closed vessel. If the stereoisomeric starting materials differ only in the configuration at the carbon atom having the hydroxyl group they can produce identical end products so that possibly racemates of such starting materials can be used instead of the optically pure compounds as starting materials.

Examples of suitable starting materials of the general formula III are 1 - phenyl - 2-amino - ethanol, 1 - phenyl - 2 - amino-propanol, 1 - phenyl - 2 - methylamino-propanol, in particular L-ephedrine, 1 - *p*-tolyl - 2 - methylamino - propanol, 1 - (*p*-chlorophenyl) - 2 - methylamino - propanol, 1 - *p* - anisyl - 2 - methylamino - propanol, 1 - (*p* - hydroxyphenyl) - 2 - methylamino-ethanol, 1 - (*m.p.* - dihydroxyphenyl) - 2-methylamino - ethanol, 1 - (*p* - hydroxy-phenyl) - 2 - *n* - butylamino - ethanol, 1-(*m.p.* - dihydroxyphenyl) - 2 - amino-propanol and 1 - (*m.p.* - dihydroxyphenyl)-2-methylamino - propanol. These hydroxy-amines can be reacted for example with propylene oxide, 1.2- and 2.3-epoxy-butane, cyclohexane oxide, glycide and its ethers such as the methyl, ethyl, phenyl, *p*-anisyl or benzyl ethers.

Also by means of the same reaction, starting materials of the general formula II are obtained by reacting a hydroxyamine of the general formula:



V

with an oxirane of the general formula:

VI

wherein Ar, R_1, R_2, R_3 and R_4 have the meanings given above. In this case too the crude products can be used direct for ring closure. Suitable hydroxyamines in this case are, for example 1-amino- and 1 -methyl-amino- 2-hydroxy-propane, 1-methylamino-2-hydroxy-3-ethoxy-propane, 1-methylamino-2-hydroxy-3-phenoxy-propane, all of which can be reacted for example with styrol oxide or trans-β-methyl styrol oxide.

Starting materials of the general formula II can also be obtained if, instead of the oxiranes of the general formulae IV or VI, corresponding halogen hydrins are reacted with hydroxy-amines of the general formulae III or V.

Finally, compounds of the general formula I in which R_3 is an alkyl or alkenyl radical containing 1 to 4 carbon atoms, are obtained by reacting morpholine compounds of the general formula:

VII

wherein Ar, R_1, R_2 and R_4 have the meanings given above, with alkylating or alkenylating agents containing 1 to 4 carbon atoms such as, e.g. alkyl or alkenyl halides, aryl sulphonic acid alkyl esters, dialkyl sulphates, or with formaldehyde in the presence of formic acid. The compounds of the general formula VII can be obtained by the first two processes above mentioned on using hydroxyamines of the general formulae III or V having a primary amino group.

The morpholine compounds of the general

formula I form acid addition salts with inorganic and organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, tartaric acid and citric acid. Some of these acid addition salts are soluble in water.

The following examples further illustrate the production of the morpholine compounds. Parts are given as parts by weight and their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

EXAMPLE 1

7.4 Parts of glycide and 16.5 parts of L-ephedrine are added to 0.5 parts of water and the whole is heated for 15 hours at 90°. After cooling, the resin is dissolved in 200 parts of ether and a solution of 9.8 parts of concentrated sulphuric acid in 100 parts of ether is added at 0°, whereupon a white semi-solid precipitate is formed. The ether is then distilled off and the residue is mixed at 0° with 100 parts of concentrated sulphuric acid. The solution obtained is left to stand for 2 to 3 hours at room temperature and then poured on to ice. After shaking out once with ether, caustic soda lye is added to the aqueous phase until there is an alkaline reaction. It is then extracted with ether, the ethereal solution is dried over potassium carbonate, the ether is distilled off and the 2 - phenyl - 3.4-dimethyl - 6 - hydroxymethyl - morpholine is distilled off in the high vacuum.

In an analogous manner:

2 - phenyl - 3.4 - dimethyl - 6 - ethoxymethyl - morpholine ($B.P._{0.05}$ 92—94°) is obtained from 16.5 parts of L-ephedrine and 10.2 parts of glycide ethyl ether;

2 - phenyl - 3.4 - dimethyl - 5.6 - tetramethylene - morpholine ($B.P._{0.02}$ 91—93°) is obtained from 16.5 parts of L-ephedrine and 9.8 parts of cyclohexene oxide;

2 - phenyl - 3.4 - dimethyl - 6 - decylmorpholine ($B.P._{0.0001}$ 139—140°) is obtained from 16.5 parts of L-ephedrine and 20.3 parts of 1.2-epoxydodecane; and

2 - (*p* - chlorophenyl) - 3 - methyl - 6-decyl - morpholine ($B.P._{0.0005}$ 150—152°) is obtained from 18.5 parts of 1 - (*p* - chlorophenyl) - 2 - amino - propanol and 20.3 parts of 1.2 - epoxydodecane.

EXAMPLE 2

16.5 Parts of L-ephedrine and 7.0 parts of propylene oxide are reacted at 80—90° for 5 hours in a closed vessel, for example in a glass tube which has been sealed by melting. As described in example 1, the reaction product is treated with concentrated sulphuric acid and worked up in the same way.

The 2 - phenyl - 3.4.6 - trimethyl morpholine boils at 71—72.5° under 0.05 mm pressure. $[\alpha]_D^{20} = +34.8°$ (c 1.349; $CHCl_3$).

Recrystallised from alcohol, the picrate melts at 167—172°.

2 - ($3^1.4^1$ - dimethylphenyl) - 3.6 - dimethylmorpholine is obtained in an analogous manner from 17.9 parts of 1 - ($3^1.4^1$ - dimethylphenyl) - 2 - amino - propanol, 6.0 parts of propylene oxide and 0.5 parts of water.

EXAMPLE 3

16.7 Parts of 1 - (*p* - hydroxyphenyl) - 2-methylamino - ethanol are dissolved at 100—110° in 100 parts by volume of dimethyl formamide and 1 part of water. 13.4 Parts of benzyl ethylene oxide are added to the solution whereupon the whole is heated for 20 hours at this temperature. After evaporating to dryness in the vacuum, the reaction mixture is dissolved in 130 parts by volume of 48% aqueous hydrobromic acid and then again evaporated to dryness in the vacuum. Water and ether are added to the residue, the whole is saturated with potassium carbonate and the morpholine derivative is obtained from the ethereal solution after drying and distilling off the ether. On crystallising from acetone/petroleum ether, the pure 2 - (4^1 - hydroxyphenyl) - 4 - methyl - 6 - benzyl - morpholine is obtained.

EXAMPLE 4

15.0 Parts of L-ephedrine, 13.5 parts of 3-phenoxy-1.2-epoxypropane and 1 part of water are warmed at 50° until a clear solution has formed. The solution is then heated for 14 hours at 100°.

25 Parts of the crude product so obtained are dissolved in isopropanolic hydrochloric acid, the solution is evaporated to dryness in the vacuum and about 0.5 parts of *p*-toluene sulphonic acid are added to the residue. The reaction mixture is then heated at a bath temperature of 170° for 10 hours under reduced pressure (30—50 mm Hg) and the water formed on ring closure is distilled off. The residue is dissolved in water, ether is added and the whole is saturated with potassium carbonate. The pure 2 - phenyl - 3.4-dimethyl - 6 - (phenoxymethyl) - morpholine ($B.P._{0.0001}$ 117—120°) is obtained from the ether extract by distillation in a Hickmann flask.

In an analogous manner:

2 - ($3^1.4^1$ - dimethoxy - phenyl) - 3 - methyl-6 - phenoxymethyl - morpholine is obtained from 21.1 parts of 1 - ($3^1.4^1$ - dimethoxyphenyl) - 2 - aminopropanol and 15 parts of 1 - phenoxy - 2.3 - epoxypropane, and 2 - (4^1-methoxy - phenyl) - 3 - methyl - 6 - vinylmorpholine is obtained from 18.2 parts of 1-(4^1 - methoxy - phenyl) - 2 - amino - propanol and 7 parts of butadiene monoxide.

EXAMPLE 5

16.5 Parts of L-ephedrine, 16.6 parts of 1 - phenylthio - 2.3 - epoxypropane and 0.5 parts of water are heated first for 3 hours at 50° and then for 14 hours at 90—100°. The

reaction product obtained is then treated at a bath temperature of 150—160° for 10 hours as described in example 4. The 2-phenyl-3.4-dimethyl - 6 - (phenylthiomethyl) - morpholine passes over at 135—138° under 0.0004 mm pressure.

EXAMPLE 6

7.6 Parts of 2 - phenyl - 5.6 - dimethyl-morpholine, 90 parts by volume of *n*-butyl alcohol, 5.5 parts of *n*-butyl bromide and 6.9 parts of pulverised dry potassium carbonate are stirred for 24 hours at 80—90°. After concentrating the reaction mixture in the vacuum, the residue is dissolved in water and the solution is extracted with ether. The ether extract is distilled through a short Vigreux column and 2 - phenyl - 4 - *n* - butyl - 5.6-dimethyl - morpholine is obtained. B.P.$_{0.001}$ 81—82°.

2 - (3¹.4¹ - dimethyl - phenyl) - 3.6-dimethyl - 4 - allyl - morpholine is obtained in an analogous manner from 11.0 parts of 2 - (3¹.4¹ - dimethyl - phenyl) - 3.6-dimethyl-morpholine, 3.8 parts of allyl chloride and 7.4 parts of potassium carbonate.

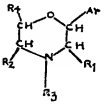
EXAMPLE 7

48 Parts of styrol oxide, 35.6 parts of 1.2-dimethyl-ethanol-amine and 2 parts of water are heated first for 3 hours at 40—50° and then for 15 hours at 80—90°. The (3-hydroxy - but - 2 - yl) - (2 - hydroxy - 2-phenyl - ethyl) - amine obtained passes over at 106° under 0.0002 mm pressure.

40 parts of this compound are dissolved in 200 parts by volume of concentrated sulphuric acid at room temperature with occasional cooling and the solution is then left to stand for 24 hours at room temperature. It is then poured into ice water, the reaction is made strongly alkaline with sodium hydroxide and the whole is extracted with ether. The 2-phenyl - 5.6 - dimethyl - morpholine obtained boils at 68° under 0.0007 mm pressure.

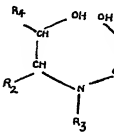
WHAT WE CLAIM IS:—

1. A process for the production of morpholine compounds having the general formula:



I

wherein Ar is an unsubstituted phenyl radical or a phenyl radical substituted by halogen atoms, alkyl, alkoxy or hydroxy groups, R_1 and R_2 are hydrogen atoms or alkyl radicals containing 1 to 4 carbon atoms, R_3 is a hydrogen atom or an alkyl or alkenyl radical containing 1 to 4 carbon atoms and R_4 is an araliphatic radical or an aliphatic radical which may contain oxygen or sulphur atoms as linking members or hydroxy groups as substituents; R_4 may also form together with the alkyl radical R_2 a divalent hydrocarbon radical, which comprises reacting a compound having the formula:



II

with dehydrating agent.

2. A process as claimed in Claim 1 in which Ar is a phenyl radical substituted by halogen atoms, alkyl, alkoxy or hydroxy groups.

3. A process as claimed in claim 1 or 2 in which R_4 is an aliphatic radical containing oxygen or sulphur atoms as linking members or hydroxy groups as substituents.

4. A process as claimed in claim 1 or 2 in which R_4 is an aliphatic hydrocarbon radical which is bound with R_2 to form a divalent hydrocarbon radical.

5. A process as claimed in any of claims 1 to 4 in which the dehydrating agent is a mineral acid.

6. A process as claimed in claim 5 in which the mineral acid is cold concentrated sulphuric acid or warm 48% hydrobromic acid.

7. A process as claimed in any of claims 1 to 6 in which the compound having the general formula II as defined in claim 1 is formed by reacting a hydroxy amine of the general formula:

III

with an oxirane having the general formula:

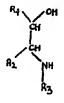
IV

wherein Ar, R_1, R_2, R_3 and R_4 have the

meanings defined in claim 1.

8. A process as claimed in claim 7 in which the reaction is carried out in the absence of an organic solvent.

9. A process as claimed in any of claims 1 to 4 in which the compound having the general formula II as defined in claim 1 is obtained by reacting a hydroxy amine of the general formula:



V

with an oxirane of the general formula:

VI

wherein Ar, R_1, R_2, R_3 and R_4 have the meanings defined in claim 1.

10. A process for the production of a morpholine compound having the general formula I as defined in claim 1 wherein R_3 is an alkyl or alkenyl radical containing 1 to 4 carbon atoms which comprises reacting a morpholine compound having the general formula:

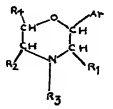
VII

wherein Ar, R_1, R_2, and R_4 have the meanings defined in claim 1, with an alkylating or alkenylating agent containing 1 to 4 carbon atoms.

11. A process as claimed in claim 10 in which the compound having general formula VII as defined in claim 10 is obtained by reacting a hydroxy amine having the general formula III as defined in claim 7 with an oxirane having the general formula IV as defined in claim 7 or reacting a hydroxyamine having the general formula V as defined in claim 9 with an oxirane having the general formula VI as defined in claim 9 wherein the hydroxy amines have a primary amino group and treating the product of either reaction with a dehydrating agent.

12. A process for the production of a compound having the general formula I as defined in claim 1 as hereinbefore described with reference to and as illustrated in the foregoing Examples.

13. Morpholine compounds having the general formula:



I

wherein Ar is an unsubstituted phenyl radical or a phenyl radical substituted by halogen atoms, alkyl, alkoxy or hydroxy groups, R_1 and R_2 are hydrogen atoms or alkyl radicals containing 1 to 4 carbon atoms, R_3 is a hydrogen atom or an alkyl or alkenyl radical containing 1 to 4 carbon atoms and R_4 is an araliphatic radical or an aliphatic radical which may contain oxygen or sulphur atoms as linking members or hydroxy groups as substituents; R_4 may also form together with the alkyl radical R_3, a divalent hydrocarbon radical, whenever produced by a process as herein described and claimed.

14. A compound as claimed in claim 13 in which Ar is a phenyl radical substituted by halogen atoms, alkyl, alkoxy or hydroxy groups.

15. A compound as claimed in claim 13 or 14 in which R_4 is an aliphatic radical containing oxygen or sulphur atoms as linking members, or hydroxy groups as substituents.

16. A compound as claimed in claim 13 or 14 in which R_4 is an aliphatic hydrocarbon radical which is bound with R_3 to form a divalent hydrocarbon radical.

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